to tighten up the arteries and diminish the systolic output of the left ventricle. In case of perforation a large dose of opium together with morphia injected subcutaneously would offer a patient the only chance.

I have now brought my address to a conclusion, and have to thank you for your patient attention. If I have in any measure succeeded in my attempt to render more clear the part played by the various morbid actions which contribute to the symptomatology of typhoid fever, and have thus made it more easy to deal with dangers as they arise or to anticipate and prevent some of them, I shall not unworthily have occupied your time and my own.

THE BACILLUS OF BUBONIC PLAGUE.[1]

BY PROFESSOR S. KITASATO.

[PRELIMINARY NOTICE.]

EARLY this year an epidemic of bubonic plague broke out in the south of China and Canton, from which city the disease was imported into the neighbouring island of Hong-Kong, where it has prevailed from the beginning of May until now. The Imperial Japanese Government sent a commission to Hong-Kong in order to study the plague, especially as regarded its bacteriological character and its pathological and clinical features. The pathology and medicine were the special study of Professor Aoyama, and the bacteriological part received the care of the writer. Having left Japan on June 5th, 1894, we arrived at Hong-Kong on the 12th of the same month. Here Dr. Lowson, Acting Superintendent of the Government Civil Hospital, put everything needful at our disposal in the most friendly spirit. A room in the Kennedy Town Hospital (one of the plague establishments) was given to us, and there we began our work on June 14th. On that day we were able to see a post-mortem examination performed by Professor Aoyama. I found numerous bacilli in the bubo (in this case a swelling of the inguinal glands), in the blood of the heart, in the lungs, liver, spleen, &c. As the post-mortem examination was made eleven hours after death I still had doubts about the true significance of what I found; I therefore made a cultivation and inoculated a mouse from a small piece of the spleen. On the same day I took, with all due precautions, some blood from the finger tips of a patient who had the disease in a very bad form, with a temperature of 40·5° C., swelling of the axillary glands, &c. Under the microscope I found bacilli with capsules, the poles of which were stained much deeper with aniline dyes than the middle part; this gave them a great likeness to the bacilli of chicken cholera (bacillus choleræ gallinarum). On the next day all the serum cultivations which were prepared in the incubator from the different organs of the body and of blood from the finger tips showed a growth of micro-organisms, which, under the microscope, were not to be distinguished from those which we found in the blood and in the interior of the bubo at the first post-mortem examination. The bacilli differed only by being a little longer and staining more easily in the middle than those taken from the blood. With these cultivations I inoculated subcutaneously mice, guinea-pigs, rabbits, and pigeons. The mice, which were inoculated on the first day with a piece of spleen and some blood from the finger tips, died in two days' time, and at the post-mortem examination upon them I found œdema round the place of inoculation, and the same bacilli in the blood, in the internal organs, and in the œdematous part around the place of inoculation. All animals which had been inoculated with the cultivations (pigeons excepted) died after periods extending from one to four days, according to the size of the animal. The same state of the organs after death and the same bacteriological observations always obtained as in the case of the mice previously referred to. I propose to give further details about my experiments on animals at a later time. Every day I took blood from many plague patients and examined it, and almost every time I found the bacilli as above described, sometimes in great numbers, sometimes only few in number, so that many glass slides had to be examined to find good specimens. On the other hand, these same bacilli were to be found at every post-mortem examination (of which we had upwards of fifteen) in great quantity in the bubonic swellings, in the spleen, the lungs, the liver, in the blood contained in the heart, in the brain, intestines—in fact, in all internal organs without exception—and every cultivation from any particle of these parts invariably produced the same bacilli. Suppose the contents of a bubo or a small piece of the spleen are rubbed on the cover-glass, and the latter, after having been stained, is examined under the microscope (one-twelfth inch oil immersion, Zeiss) bacilli will be discovered in the form found in pure cultivation (Reinkultur). In the spleen especially the bacilli are aggregated in heaps. Bacilli from bubonic swellings and from other internal organs are more easily stained with aniline dyes in their middle part than those taken from the blood, but any serum cultivation prepared from them produces the same form of bacillus. In any case where cultivations are prepared from parts of any internal organs or from the blood taken from the finger tips, with careful observation of all due precautions, pure cultivations (Reinkultur) of one and the same bacillus are always obtained; therefore the most intimate connexion must exist between the bacillus and the disease. Full particulars about the observations at the post-mortem examinations will be given later by my colleague Professor Aoyama; generally it may be said that the parts in the neighbourhood of the bubo were œdematous, of a colour between black and red, infiltrated with gelatinous exudation, and that the spleen was enlarged. Both phenomena are to be found in inoculated animals in which the parts round the place of inoculation present the same œdematous exudations as are found in human beings.

I will now give a few short notes about the bacillus. The bacilli are to be found in the blood, in the buboes, in the spleen, and in all other internal organs of the victims of plague. The bacilli are rods with rounded ends, which are readily stained by the ordinary aniline dyes, the poles being stained darker than the middle part, especially in blood preparations, and presenting a capsule sometimes well marked, sometimes indistinct. The bacilli found in the spleen are best stained by a solution of methyl blue. I am at present unable to say whether or no "Gram's double-staining method" can be employed. I shall report upon this on a future occasion. The bacilli show very little movement, and those grown in the incubator, in beef-tea, make the medium somewhat cloudy. The growth of the bacilli is strongest on blood serum at the normal temperature of the human body (34° C.): under these conditions they develop luxuriantly and are moist in consistence and of a yellowish grey colour; they do not liquefy the serum. On agar-agar jelly (the best is good glycerine agar) they also grow freely. The different colonies are of a whitish-grey colour and by a reflected light have a bluish appearance; under the microscope they appear moist and in rounded patches with uneven edges—at first they appear everywhere as if piled up with "glass-wool," later as if having dense, large centres. If a cover-glass preparation is made from a cultivation on agar-agar, and, after having been stained, is observed under the microscope long threads of bacilli are seen, which might, by careless inspection, be mistaken for a coccus chain, but are recognised with certainty as "threads of bacilli" under closer observation. The growth on agar-gelatine is similar to that on agar-agar; in a puncture cultivation at the ordinary temperature after a few days they are found growing as a fine dust in little points alongside the puncture, but with very little growth on the surface. Whether these bacilli are able to liquefy ordinary gelatine or not I am at present unable to decide, as the temperature of Hong-Kong ranges so high that the employment of simple nutritive gelatine is out of the question. I shall give further information on this question later. On potatoes at a temperature of from 28° to 30° C. there was no growth after ten days' observation, but at a temperature of 37° C. the bacilli developed sparingly after a few days; they were whitish grey in colour and exsiccated. As mentioned before the bacilli grow best at a temperature of from 36° C. to 39° C.; at how low a temperature growth is possible I am unable at present to state. So far I have been unable to observe the formation of spores.

Experiments on animals.—Mice, rats, guinea-pigs, and rabbits are susceptible to inoculation. If these animals are inoculated with pure cultivations, or with the blood of a plague patient in which the bacilli have been observed, or with the contents of a bubo, or with pieces of internal organs, or even with the contents of the intestine, they begin to

[1] In connexion with this paper, for forwarding which to us we have to thank Dr. James A. Lowson, of Hong-Kong, our readers are referred to the illustrations of the bacillus which were published in THE LANCET of August 11th, 1894.

become ill in from one to two days, according to the size of the animal. Their eyes become watery, they begin to show disinclination for any effort, later they avoid their food, and hide quietly in a corner of the cage. The temperature rises to 41·5° C., and with convulsive symptoms they die in from two to five days. I must observe that in Hong-Kong I could only obtain small guinea-pigs (weight from 100 to 150 grammes) and small rabbits (from 200 to 250 grammes). If I could have experimented upon larger animals it is possible that life would have been prolonged somewhat beyond the periods mentioned above. The parts around the point of inoculation are infiltrated with a reddish gelatinous exudation, the spleen is enlarged, sometimes there is a swelling of the lymphatic glands, and in all the organs the bacilli are found. The results found after death in animals are very similar to those found in anthrax and in œdema malignum. Pigeons do not appear to be susceptible to the influence of bacilli. I made experiments by feeding some mice and guinea-pigs with pure cultivations of the bacillus and with small pieces of the internal organs: the result was such animals perished in a few days under the same symptoms as those which had been inoculated. In all the internal organs of animals so destroyed I found the bacilli. With the dust of dwelling-houses from which the plague-stricken had been removed I made several experiments upon animals. Some of the animals died from tetanus. In one case only a guinea-pig died with plague symptoms, and in this animal the same bacilli were found in the internal organs as in those of plague patients who had succumbed. These experiments with the dust from infected houses I shall certainly continue. Many rats and mice at present die spontaneously in Hong-Kong. I examined some of them. In the internal organs of a mouse I discovered the same bacilli.

POWER OF RESISTANCE OF THE BACILLI TO PHYSICAL AND CHEMICAL AGENCIES.

Experiments with desiccation.—The contents of a bubo in which the bacilli were present in great numbers were wiped over cover-glasses (perfectly cleansed by heat and alcohol), and some of these cover-glasses were dried in the air of a room at a temperature ranging from 28° to 30° C. Others I exposed directly to the sun's rays, and from among them, after an exposure of from one, two, and three hours up to six days, I removed some parts, putting such portions in beef-tea and placing them in the incubator. Those which had been standing in the room from one to thirty-six hours showed a pretty good growth in the incubator, but those which had been in the room for more than four days were unable to show any growth even after one week's incubation. Those exposed directly to the sun were all destroyed after from three to four hours. Further cultivations on serum were treated exactly like the contents of the bubo with very similar results.

Experiments with heat.—Beef-tea cultivations which had been heated for thirty minutes in a water bath up to 80° C. were destroyed; at 100° C. in the vapour apparatus they were destroyed in a few minutes.

Chemicals.—Carbolic acid: To every 10 cubic centimetres of beef-tea cultivations, which had been standing in the incubator for from two to three days and had grown well, carbolic acid was added of a strength of ½ per cent. of the whole, ¾ per cent., and 1 per cent. They were afterwards well shaken, and left at the ordinary temperature of the room. Of each of these cultivations a few drops were brought into sterilised beef-tea after one, two, and three hours and left in the incubator, with the following results. Those cultivations which contained ½ per cent. and ¾ per cent. carbolic acid and had been left standing in the room for one hour, grew in the incubator after two days. A cultivation, however, of 1 per cent which had been left standing for only one hour did not grow even after one whole week in the incubator. Cultivations that had been mixed with only ½ per cent. of carbolic acid and had been left standing for more than two hours did not show growth after one week in the incubator, neither did the other cultivations containing a greater percentage produce any growth. Quicklime: Experiments were made with quicklime in exactly the same way as with carbolic acid, with the following results. Those beef-tea cultivations which contained ½ per cent. of quicklime grew sparingly after two hours; those containing 1 per cent. of quicklime ceased to grow. Cultivations which had been mixed for more than three hours, even if containing only ½ per cent. of quicklime, showed no growth. Further experiments with chemicals should have been made, but as my time was extremely limited I had to leave them to a future time.

The following is a short review of the Plague generally. History shows us that plague epidemics existed in the fourteenth century both in Asia and Europe, and thousands of human beings perished. Since then from time to time, now here, now there, an epidemic has appeared, and until lately the disease almost seemed to have vanished from the face of the earth. This, however, was not so. In China it has existed to this day, especially in Yun Nan, where it occurs every year in an endemic form. From the latter place it was imported to Canton, and from Canton for the first known time it has reached Hong-Kong. The recent outbreak has given us opportunity for studying this disease—a cause of mystery for centuries—with the means which modern science places in our hand. The principal symptoms of the disease now ravaging Hong-Kong are the following. After the period of incubation, which lasts from three to five days (possibly a little longer, and some medical men say as long as eight days), the patient complains of high fever and swelling of one or more of the lymphatic glands (buboes). These swellings may antedate, coincide with, or follow the rise in temperature, and are accompanied by severe pain. The gland most commonly affected is one of the femoral chain; next an inguinal, next axillary, and sometimes a cervical gland is affected. The tongue is coated with a greyish-white or dark brown heavy fur. There is commonly headache, also delirium, the heart is generally affected, and occasionally vomiting and diarrhœa are present (not frequently the two last conditions, which are generally forerunners to a fatal issue). In patients who survive the onset of the disease the temperature does not fall until a week has passed, and convalescence is a slow process. Sex and age make no difference in the disease—men and women, infants and old people, are attacked equally. If in such a case as described the blood be examined the before-described bacilli in greater or lesser numbers will be found present. (In thirty patients I obtained twenty-five positive results, and two of my subjects which were without bacilli were subsequently proved not to be suffering from the plague at all.) As indicated before, it is not always an easy matter to demonstrate the presence of the bacilli directly in the blood of many patients—they are present sometimes in such small numerical strength that only after examining several slides can they be discovered. In order to be safe, not only must the blood of a suspected plague patient be examined, but a cultivation should also be made. In the buboes the bacilli always occur in the form of pure cultivations, but it is obviously not always easy to procure a specimen of bubo contents from the living subject. The question arises, Is it possible to make a diagnosis of bubonic plague from examination of the blood of the suspect? In many cases, Yes. But a good deal of bacteriological practice is required, or such diagnosis is impossible. It is a well-known fact that so far, amongst infectious diseases produced by bacilli, only two micro-organisms have been found in human blood—viz., the bacillus of anthrax and the spirochæta of relapsing fever (we do not include the plasmodia of malaria). Here in the blood of human beings suffering from bubonic plague we have a new bacillus possessing the following qualities: (1) this bacillus occurs in the blood, in buboes, and in the internal organs of the plague-stricken only; (2) this bacillus is not to be found in any other infectious disease; (3) with this bacillus it is possible to produce in animals the identical symptoms which the disease presents in human beings. From this evidence we must come to the conclusion that this bacillus is the cause of the disease known as the bubonic plague; therefore the bubonic plague is an infectious disease produced by a specific bacillus. What are the channels by which these bacilli enter the human body? We may suppose that they have three principal channels of entrance: by respiration, through an external wound, and by the intestinal tract. Examples of the first two ways, of which I shall speak later, are abundant. Examples of the last-mentioned way are not positive so far; but, considering that we discovered the bacilli in the intestinal canal and experiments on animals prove that feeding alone produces definite results, the concession must be made that the third is a possible method of infection. Most of the cases of bubonic plague occur amongst the Chinese, a few other nationalities excepted. Whoever has looked into a Chinese dwelling in Taipingshan is at once persuaded that here is a suitable hunting-ground

for the plague bacillus. The houses are so filthy that they are unfit for human habitation. What means are to be employed against the plague?—preventive measures, general hygiene, good drainage, perfect water-supply, cleanliness in dwelling-houses, and cleanliness in the streets. As soon as an epidemic breaks out the sick must be perfectly isolated. The infected dwellings, before the household things are removed, have to be disinfected by a 2 per cent. carbolic acid solution or by a solution of quicklime in a correct way. Afterwards, wearing apparel, linen, bedding, &c. should be specially disinfected by a steam disinfector for one hour at a temperature of 100° C.; should a steam disinfector not be available the things ought to be exposed directly to the sun's rays for several hours. Articles unfit for use ought to be burned. Dwelling-houses thus emptied should be cleansed again with quicklime or carbolic acid. The fæces should be disinfected carefully with quicklime. Dead bodies covered with quicklime are either to be burned or to be buried at least three metres from the surface. Mice and rats which have died spontaneously in dwelling-houses should be carried away with proper precautions. After a patient has apparently recovered he must be kept apart from the healthy community for a period of a month, for during convalescence the bacilli may be discovered in the blood from three to four weeks after all symptoms have ceased. Individuals ought to keep away from plague patients and infected houses, and should be careful about their solid and liquid nourishment. These measures have been generally in force during the epidemic in Hong-Kong. The question as to whether immunity against the bacillus of plague is possible on the lines practised against many other bacillary infectious diseases remains at present an open one. I shall study it thoroughly later and in an exhaustive manner. All that I have described above must be regarded only as a short preliminary notice. The results of extensive study on the subject of the plague bacillus will be published by me at a later time. Before I conclude this notice I beg to tender my heartiest thanks to the Colonial Government of Hong-Kong, to all the medical men here, and especially to Dr. Lowson for his kind assistance.

Hong-Kong, July 7th, 1894.

ON THE

IMPROBABILITY OF A PARASITIC ORIGIN OF MALIGNANT DISEASE.

BY RICHARD BARWELL, F.R.C.S.ENG.,
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IN my last paper on this subject[1] I adduced many cogent facts in the clinico-pathological history of malignancy which are incompatible with the supposition of its parasitic origin. Among these was its incommunicability. Every disease which is known to be due to any form of microbe is contagious, infectious, or epidemic, and possesses at least two, sometimes all three, of these qualities. This holds good not merely of zymotic fevers, but also of such specific diseases as syphilis, tubercle, glanders, leprosy, actinomycosis, and some others.[2] But malignancy, though there may be theoretical reasons for considering that it may be infectious,[3] has, as has been seen, clinically shown itself to be non-infectious and non-inoculable—indeed non-communicable; nor is that negative quality proved merely by clinical experience. Innumerable experiments have, with very few exceptions, shown the intense difficulty—but for these rare exceptions, of which more must be said by-and-bye, I might have said the impossibility—of propagating malignancy from a so diseased person or animal to a healthy one. Some account of these attempts will be given immediately, but the ground must first be cleared of a possible source of fallacy. Even if every attempt at transferring cancer from a diseased subject (human or animal) to a healthy one had succeeded, such success would in no wise prove the existence of a cancer-producing parasite, because a few cells or nuclei from a malignant tumour (having found congenial soil) would be quite as likely to give rise to a carcinoma as any imaginable parasite—indeed, much more likely, for such cells or nuclei would proliferate in that soil and propagate their own species, and that whatever the tissue in which they were deposited might be. But it is inconceivable that a parasite pure and unmixed with tumour-elements, emanating, for instance, from an epithelioma and deposited in a region void of epithelial cells should by its irritation produce there a neoplasm consisting of that particular sort of cell. Whence could the parentage of such cells be derived? Therefore, though success would prove little or nothing, a very large percentage of failures must go far to prove the non-existence of a cancer-producing microbe, because it is not conceivable that such a being could find so many victims, human and animal—in other words, could, unaided, so readily penetrate living tissues, and yet, when artificially introduced in hundreds of different ways, should persistently refuse to survive and to follow out its life-history. That is, it is inconceivable unless one imagines that only an immature form of the parasite, which cannot be produced within the animal body,[4] is the only form of the problematical microbe that can infect.

The experiments referred to, which have been practised more or less for at least a hundred years, but of late have been carried on with great perseverance and frequency, take principally five forms: (1) from a diseased human being to a healthy one; (2) from a diseased part to a healthy part of the same subject; (3) from disease in the human subject to an animal; (4) from a diseased animal to a healthy one of the same species; and (5) from a diseased animal to a healthy one of a different species. The mode of experimentation, especially in the last three classes, has been varied in every imaginable manner—as to the animals chosen, the method of attempted infection, the state and kind of material introduced, the sort and condition of receptive tissue, &c.—the most important variant, as eliminating a large element of failure, being the introduction of asepsis.

1. It is self-evident that, if inoculation of a healthy person from a malignant tumour has been proved to be entirely harmless, repetition of the experiment is useless; if it has not been so proved it is unjustifiable. Nevertheless in 1808 Alibert inoculated with the succus from a mammary cancer three students of the Hôpital St. Louis, and about a week later he inoculated Dr. Biet and himself. Dr. Biet suffered from a pretty sharp attack of lymphangitis (septic inoculation); all the other subjects suffered little or nothing.

2. Auto-inoculation and grafting of cancerous nodules from one part to another of a patient's body has a large percentage of success, as would be expected from observation of the methods by which malignant tumours infiltrate and spread, from the existence of contact and especially of continuity nodules; the meaning of these easy successes will be explained hereafter.

3. Inoculation and transplantation of cancer from man to one of the lower animals has never been successful. Dr. L. Pfeiffer, indeed, states[5] that he took from a woman aged twenty-eight, suffering from secondary cancerous tumours and cachexia, a small portion of carcinoma and transplanted it into a mouse at the root of the tail; that this mouse developed a melanoma, from which he transplanted minute pieces into twelve other mice; and that of these one developed a like cancer. This statement must be left to take care of itself; had it been reliable it would have changed the whole aspect of the question and certainly would have excited much comment and imitation. Other experimenters have for a time imagined that they have achieved success, for the implanted piece has not only survived, but has increased, or has appeared to do so, then has stopped its growth, has diminished, and disappeared[6]—i.e., has been absorbed. Mr. Shattock (Morton Lecture) likens these grafts to the Hunterian implanting of a tooth in a cock's comb—that is probably a just comparison; but the human tooth was not absorbed.

4. This class of attempts—viz., inoculation or transplantation from animal to animal of the same species—has had a certain number of successes, a number which can be counted on the fingers of one hand, while the failures are almost innumerable. The cases to be reckoned as successful (and even some of these are not entirely free from doubt) are five. They are as follows. 1. Klenche's[7] inoculation of a horse from a

[1] THE LANCET, July 28th, 1894.

[2] In his Morton Lecture Sir J. Paget is reported to have said of the above diseases: "Virchow classes them with the granulomata." This is, however, only a part of Virchow's nomenclature; he really calls them "infectious granulomata." The omission of this very important adjective is, of course, due to typographical inaccuracy.

[3] See Morton Lecture by Mr. Shattock, THE LANCET, May 19th, 1894.

[4] Metchnikoff's theory, to be referred to hereafter.

[5] Die Protozoen als Krankheitserreger; second edition, p. 204.

[6] I do not propose to quote all the examples I have collected; they certainly do not exhaust the list, for many hundreds of such experiments have been published, and doubtless as many, just because they have been resultless, have not been made known.

[7] Archives de Médecine, 7ème Série, tome xv., p. 433.